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Accepted Manuscript

Clinical and laboratory predictors of deep vein thrombosis after acute stroke; Does D-dimer really improve predictive power? QUERY id="Q2" name="DVILLALON" Article title has been modified. Please check if correct and amend if necessary.

Ibrahim O. Balogun FRCP, MD (Res), Lara N. Roberts FRCPATH, MD (Res), Roopen Arya FRCPATH, PhD

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*Corresponding Author: Ibrahim Balogun, FRCP, MD (Res)

Corresponding Authors Institution:

*Department of Stroke Medicine, East Kent Hospitals University NHS Foundation Trust, East Kent, UK.

†King's Thrombosis Centre, Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, UK.

Order of Authors: *†Ibrahim O. Balogun, FRCP, MD (Res), †Lara N. Roberts, FRCPATH, MD (Res), † Roopen Arya, FRCPATH, PhD.

Dear Editor,

We thank Kola and colleagues for their interest in our work titled 'Clinical and laboratory predictors of deep vein thrombosis after acute stroke' recently published in Thrombosis Research (1). We are grateful for their thoughtful comments around the study methodology and data presentation (2).

The debate regarding meaningful outcomes in venous thromboembolism (VTE) research is a longstanding one. We acknowledge the controversy on whether distal DVT is a valid surrogate outcome measure for symptomatic major VTE. We must keep in mind the natural history of DVT which usually arises from calf veins and may resolve spontaneously, or can propagate to proximal veins, with subsequent embolisation in pulmonary vasculature without necessarily manifesting clinically obvious symptoms (3-5). The possible lack of classical symptoms of VTE informed our decision to choose asymptomatic DVT as the study outcome (1).

We acknowledge Kola and colleagues' comments regarding the methodology, particularly on the approach to creation of a prediction model. We set out to identify the relationship

between DVT and individual factors measured, including thrombin generation (a novel haemostatic marker), with subsequent aim of examining the independent role of identified factors on DVT prediction. This was achieved through logistic regression, with a stepwise process of backward selection to retain only statistically significant variables.

Wells' score was considered in our study design. However, it was developed and validated as a tool for symptomatic DVT, not for screening asymptomatic patients (6). Thus we selected simple, validated stroke severity and functional disability rating scales such as National Institute of Health Stroke Scale (NIHSS) and Barthel index (7-9), and thrombin generation, alongside D-dimer as clinical and laboratory factors respectively.

In table 4, due to multimodal distribution of D-dimer, dichotomisation was undertaken, with subsequent adjustment for confounding variables. This step was necessary in view of dose dependent relationship identified between D-dimer and DVT. The clinical variables shown were adjusted for age. Similarly, D-dimer values at stated cut-points (50th, 75th and 90th centiles) were adjusted for age, BMI, Barthel index and NIHSS. We thank Kola *et al* for bringing to our attention discrepant p-values and confidence intervals within table 4. The original data has been reviewed and transcription errors identified which have been corrected in a *corrigendum* notice submitted to the Editor.

We acknowledge that the study is limited by significant attrition due to strict exclusion criteria, thus limiting the effect of sample size on results. This is evident in the relatively high dispersion in sample distribution and wide confidence intervals observed.

We suggest that using clinical VTE as a study outcome after stroke not only at risks of being confounding with common post stroke complications stated above, but also the risk of delays in establishing an objective diagnosis. Also, whilst the discriminatory role of D-dimer in DVT is established, this has to be interpreted cautiously, especially in the aftermath of acute stroke (1, 10). We concur that external validation of D-dimer in DVT prediction post stroke is required and acknowledge this in the original publication (1)

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Table 4, Unadjusted and adjusted odds of association of clinical and laboratory predictors of DVT

Outcome	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value.
Age	3.11(1.70-4.10)	0.02	1.89 (0.67-6.69)	0.20
BMI*	4.90 (1.87-6.66)	0.05	3.20 (0.97 -4.89)	0.16 [†]
Barthel index**	5.1 (2.67-8.90)	0.018	4.2 (0.76 - 8.40)	0.15 [†]
NIHSS***	3.6 (1.03-9.11)	0.017	2.81 (0.73-8.33)	0.19 [†]
D-dimer1(Crude)	8.11 (1.90, 34.7)	0.005	-	
DD1 ≥1500ng/mL (median)	4.10 (1.39-7.40)	0.006	2.95 (1.98-5.60)	0.005 ^{††}
DD1 ≥4940ng/mL (75 th centile)	5.82 (1.72-8.40)	0.003	3.98 (2.10-9.80)	0.005 ^{††}
DD1 ≥7600ng/mL (90 th centile)	6.91 (1.84-10.2)	0.005	3.4 (1.17-11.4)	0.003 ^{††}
Log DD2	4.32 (1.23-14.3)	0.03	3.9 (1.91-7.93)	0.02 ^{††}
DD2 >500ng/mL	5.3 (1.80-13.9)	0.004	3.45 (0.76-9.40)	0.17 ^{††}

OR, odds ratio; CI, confidence interval; BMI, body mass index; DD1, D-dimer (baseline) time 1; DD2, D-dimer (week 2) time 2; NIHSS, National Institute of Health Stroke Scale; (*) per 10mg/kg increase in BMI;(**) per 4 unit decrease in Barthel index; (***) per 4 unit increase in NIHSS; (**†**) **adjusted for age, per 10 year increase in age**, (**††**) **adjusted for age, NIHSS, BMI, Barthel index**; Log, logarithm [analysis was on the log scale (base 10)].